original claims 1 and 2. No new matter is inserted into the application.

Specification

The Examiner objects to the instant abstract for being two paragraphs and over 250 words. Applicants respectfully traverse. Reconsideration and withdrawal thereof is requested. In response to the Examiner's remarks, Applicants submit an amended abstract that is in proper format according to MPEP § 608.01(b). Thus, the instant objection is overcome.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejects claims 1, 4, 5, and 11 under 35 U.S.C. § 112, second paragraph, for being indefinite. Claims 1 and 11 are canceled thus rendering the rejection applied to said claims moot. The rejection applied to the pending claims is respectfully traversed. Reconsideration and withdrawal thereof is requested.

Claims 4 and 5

Specifically, the Examiner rejects claims 4 and 5 for containing improper Markush language. In response to the Examiner's remarks, Applicants amend claims 4 and 5 as suggested by the Examiner. Thus, the instant rejection is overcome.

Issues Under 35 U.S.C. § 103

The Examiner rejects claims 1-12 under 35 U.S.C. § 103(a) for allegedly being obvious over Orion-Yhtyma Oy '075 (WO0113075), Terouanne et al. (*Analytical Biochemistry*, 1992) and Levi et al. (*Cancer Research*, 1991). Claims 1 and 11 are canceled, thus rendering the instant rejection applied to said claims moot. The rejection applied to these pending claims is respectfully traversed. Reconsideration and withdrawal thereof is requested.

The present invention

The present invention relates to a nucleic acid assay useful for detecting, identifying or quantifying a genetic mutation or polymorphism. The advantage of the present invention is that it can detect minute amounts of a test nucleic acid in a large amount of related or similar nucleic acids.

Orion-Yhtyma Oy '075

Orion-Yhtyma Oy '075 discloses a method for identifying specific point mutations and genetic variations. The method involves primer extension and incorporation of detectable NTPs in the detection step. Specifically, in the method of Orion-Yhtyma Oy '075, primers are designed that span the region on the

3′ end from the variable nucleotide. Then, labeled NTPs are added to a reaction mix, and the incorporation of a label into the primer is measured. Because the method of Orion-Yhtyma Oy '075 is basically a primer extension, it only works with single-stranded DNA. Thus, Orion-Yhtyma Oy '075 fails to disclose double-stranded DNA.

Levi et al.

Levi et al. discloses a modified PCR strategy for detecting a K-*ras* oncogene mutated at codon 12 in the presence of 1000 normal alleles, therefore improving sensitivity of the assay. Levi et al. discloses that the method can detect mutations that are present in less than 10% of the cells. Levi et al. fails to disclose a method for determining any mutant gene other than the K-*ras* oncogene mutation at codon 12.

Terouanne et al.

Terouanne et al. discloses a method for detecting a single base substitution in a DNA sequence via competitive hybridization. Terouanne et al. fails to disclose a method for determining a mutated sequence when the sequence comprises less than 10% of the entire DNA sequence.

Distinctions between the present invention and the cited references

Applicants submit that the presently claimed invention is not *prima facie* obvious over the cited references. The Examiner states that it would have been obvious to combine the disclosures of the cited references to produce the present invention. Specifically, the Examiner argues that "it would be *prima facie* obvious to one of ordinary skill in the art…to combine the teachings of Levi et al. regarding a nucleic acid assay method…with the teachings of Orion-Yhtyma Oy '075 and Terouanne et al." Applicants respectfully disagree. In fact, careful review of the cited references clearly shows that the cited references fail to disclose or suggest all of the claimed features of the present invention.

The closest prior art, as disclosed in the instant specification, is that of Terouanne et al. However, the method of Terouanne et al. is not useful for detecting a minute amount of a mutant or polymorphic gene in a large amount of related or similar nucleic acids. As evidence of this fact, Terouanne et al. states,

> "However, small amounts (<10%) of mutated sequence mixed with normal sequence could not be identified using this method since 100% homoduplex formation was not obtained when probe and target differed by a single base substitution. Moreover, the coefficient of variation calculated on data obtained from the same PCR products but from different incubations was from 7 to 8% and did not

permit detection of low percentages of mutated sequence" (see page 198, column 2, paragraph 6).

Thus, Terouanne et al. teaches away from the present invention by clearly stating that the method is not useful for quantifying small amounts of mutated or polymorphic DNA in a large amount of related or similar nucleic acids. In contrast, the present invention allows for the detection small amounts of mutated or polymorphic DNA in a large amount of related or similar nucleic acids.

Further, the addition of the Levi et al. reference to Terouanne et al. would destroy the present invention. Levi et al. uses a restriction digest to determine whether or not a sample possesses the K-*ras* oncogene mutation at codon 12. If a restriction digest were added to the present invention, for example, if the labeled standard DNA were digested, then the label and the site capable of binding to a solid support would be separated. As such, it would be impossible to determine the amount of labeled standard DNA that has bound to the solid support.

Finally, the method of Orion-Yhtyma Oy '075 is a primer extension that must use single-stranded DNA. It is well known in the art that a primer extension experiment cannot use double-stranded DNA as a template. As such, it would be impossible to combine this reference with the prior two references.

The Examiner fails to make a *prima facie* case of obviousness in the present application. Specifically, the combination of the cited references still fails to support every feature of the instant claim 13. Specifically, the combination of the cited references still fails to provide a method to quantitatively detect the proportion of a mutant/polymorphic gene within a sample containing a large amount of related or similar nucleic acids.

Overall, for all of the above reasons, the present invention possesses significant patentable features that the cited prior art does not possess. Therefore, applicants submit that all of the present claims define patentable subject matter such that this application should be placed into condition for allowance. Early and favorable action of the merits of the present application is thereby respectfully requested.

If the above amendments for some reason do not place the present application into a condition for allowance, the Examiner is respectfully requested to contact Kristi L. Rupert, Ph.D. (Reg. No. 45,702) to arrange for a personal interview in order to expedite prosecution of the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and further replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any

credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By: John M Murphy #32,807

Gerald M. Murphy, Jr.
Reg. No. 28,977
P.O. Box 747
Falls Church, VA 22040-0747
703-205-8000

GMM/KLR/csp
171-613P